Neuroanatomy, Neurology and Bayesian Networks

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Outline

1. **Introduction**

2. **Neuroanatomy: neurons and dendritic trees**
   - 'Gardener' classification of neurons
   - Bayesian networks to model consensus among experts
   - Computer simulation of dendritic morphology

3. **Neurology: Parkinson and Alzheimer**
   - Dementia: Prevalence, cost and investment in research
   - Knowledge discovery in Alzheimer's disease
   - Multi-dimensional classification for EQ-5D from PDQ-39 in Parkinson's disease

4. **Conclusions**

Outline

1. Introduction
2. Neuroanatomy: neurons and dendritic trees
   - 'Gardener' classification of neurons
   - Bayesian networks to model consensus among experts
   - Computer simulation of dendritic morphology
3. Neurology: Parkinson and Alzheimer
   - Dementia: Prevalence, cost and investment in research
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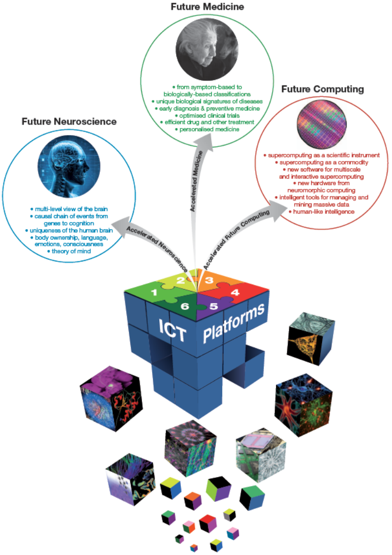
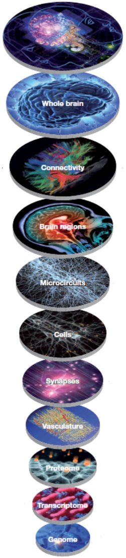
4. Conclusions

Cajal Blue Brain Project

- At the end of 2008, **Universidad Politécnica de Madrid (UPM)** and **Instituto Cajal (IC)** from the Spanish Research Council, until 2018
- UPM: data analysis, optimization, image analysis and visualization
- IC: morphology and function of neuronal cells

Human Brain Project

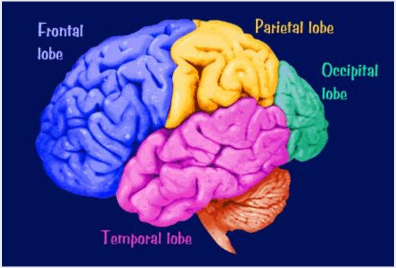


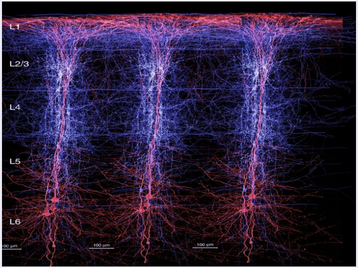


The BRAIN initiative

The human brain

Brain lobes and layers

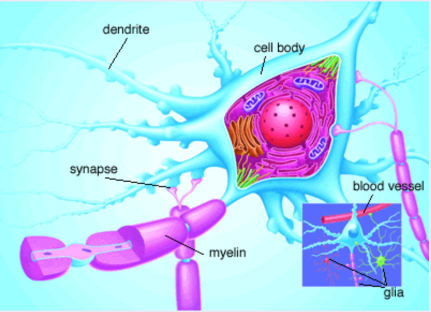




- Weight = 1.3kg, width = 140mm, length = 167mm, height = 93mm

The human brain

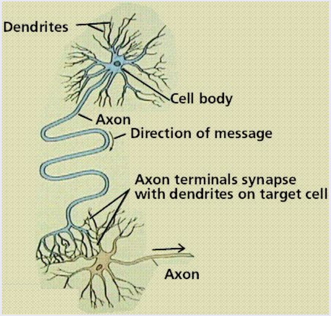
Brain at microscopic level



- Composed of neurons, blood vessels, glial cells
- Neuron is the basic structural and functional unit of the nervous system –neuron doctrine– (S. Ramón y Cajal, late 19th century)
- Just 4 microns thick → could fit 30,000 neurons on the head of a pin
- ∼86,000 million neurons (more than known stars in the universe)

The neuron

3 parts of a neuron: dendrites, soma and axon

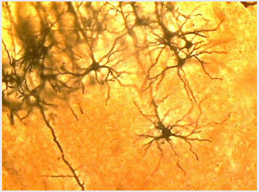


- Axons fill most of the space in the brain $\rightarrow$ >150,000 km in the human brain!!
- Each neuron connected to 1,000 neighboring neurons
- 10,000 synaptic connections each

Observing the neurons

Optical (or light) microscope. Stain the tissue

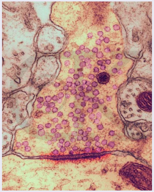
Magnify image up to 2000 times



Golgi's method (1873)

Modern electron microscope

Magnify image up to 2 million times

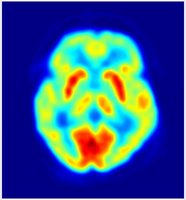


3D from multiple 2D images

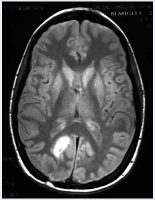
“Visualizing” mental activities from brain images

Electrical activity directly or indirectly

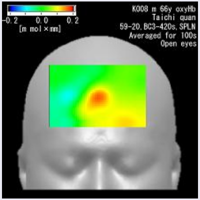
Electroencephalography (EEG)



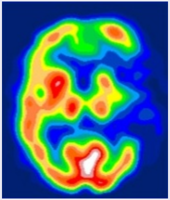
Positron Emission Tomography (PET)



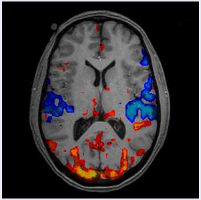
Magnetic Res. Imaging (MRI)



Functional NIR Spectroscopy (fNIRS)



Single Photon Emission Computed Tomography (SPECT)



Functional MRI (fMRI)

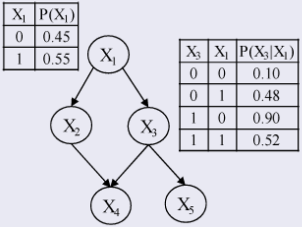
Introduction

Bayesian networks

- Graphical models used for knowledge representation and probabilistic reasoning under uncertainty

- A Bayesian network consists of two components

1. Graphical structure $\mathcal{G}$ is a directed acyclic graph (DAG)
   - *Vertices* $\rightarrow$ variables
   - *Directed edges* $\rightarrow$ conditional dependences
2. Set of parameters specifies the set of conditional probability distributions

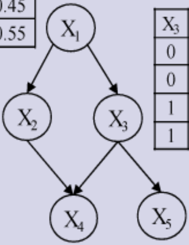


- Joint probability distribution: $P(x_1, \ldots, x_n) = \prod_{i=1}^{n} P\big(x_i \mid \mathbf{pa}(x_i)\big)$

Introduction

Bayesian networks

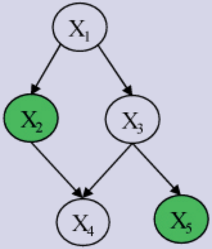
X_1	$P(X_1)$
0	0.45
1	0.55



X_3	X_1	$P(X_3 \mid X_1)$
0	0	0.10
0	1	0.48
1	0	0.90
1	1	0.52

Bayesian network learning

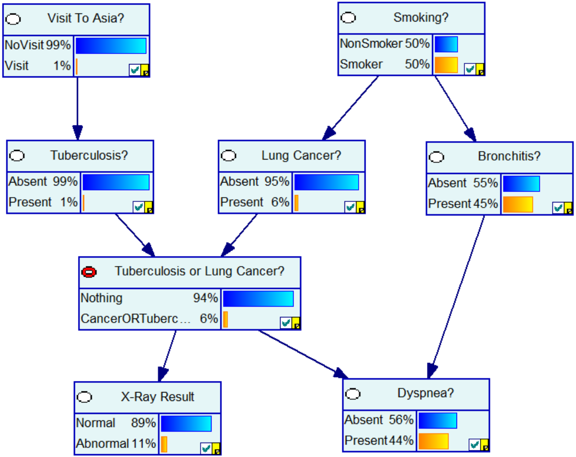
- Structure learning
- Parameter learning



Probabilistic inference

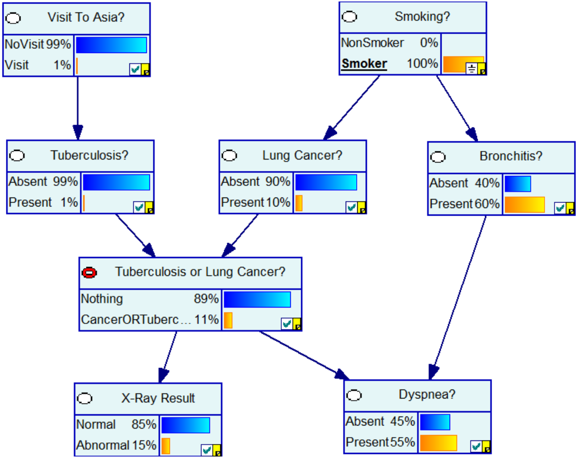
- Compute the conditional probability $P(Query \mid Evidence)$

Example of inference with network *Asia*



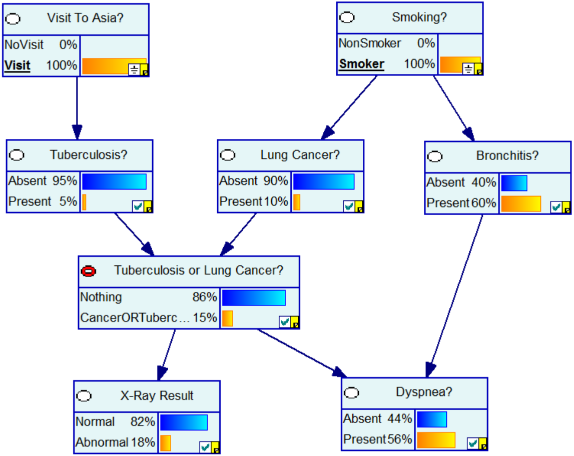
No evidence

Example of inference with network *Asia*



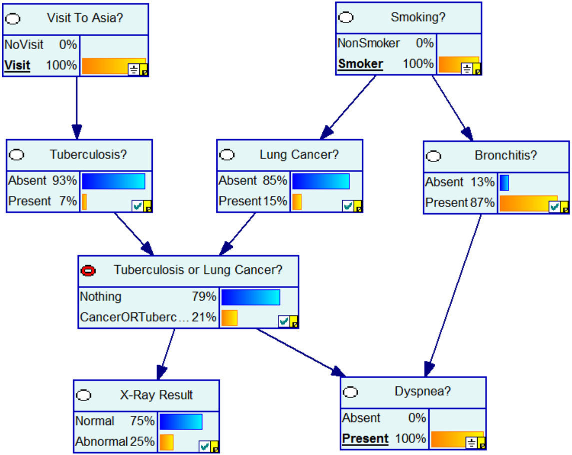
Evidence: "Smoker = yes"

Example of inference with network *Asia*



Evidence: "Asia = yes, Smoker = yes"

Example of inference with network *Asia*



Evidence: "Asia = yes, Smoker = yes, Dyspnea = yes"

Outline

Classifying and naming neurons

Do we have an accepted catalog of neuron types and names?

Outline

Classifying and naming neurons

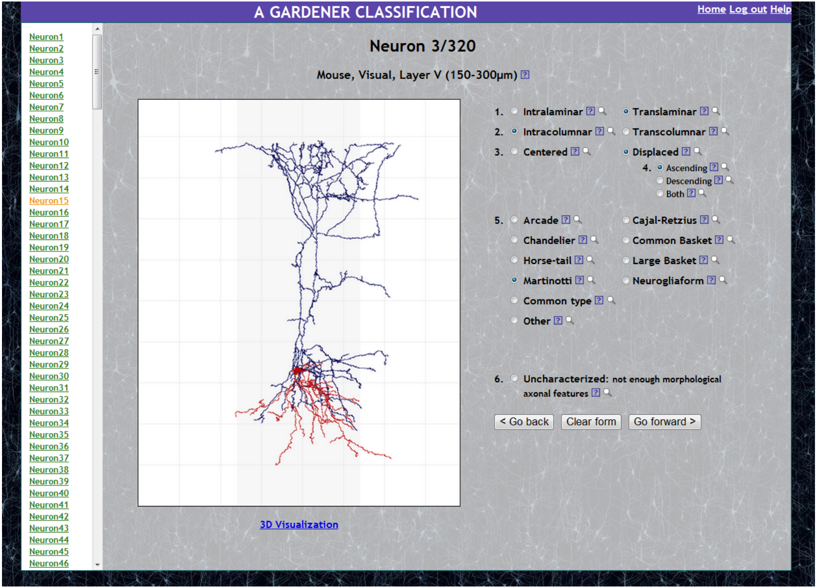
- An accepted catalog of neuron types and names, a debate for over a hundred years since S. Ramón y Cajal
- Amount of data has grown rapidly; better staining methods ⇒ harder classification
- Need of a consistent terminology for an effective communication and data sharing [Petilla Terminology, Ascoli et al. (2008)]
  - Agreement: pyramidal neuron, non-pyramidal, interneuron, chandelier (clear morphological attributes)
  - Disagreement: double bouquet, basket, Martinotti...
  - Virtually every neuroanatomist has his own classification scheme and neuron terms

A ‘gardener’ classification of neurons

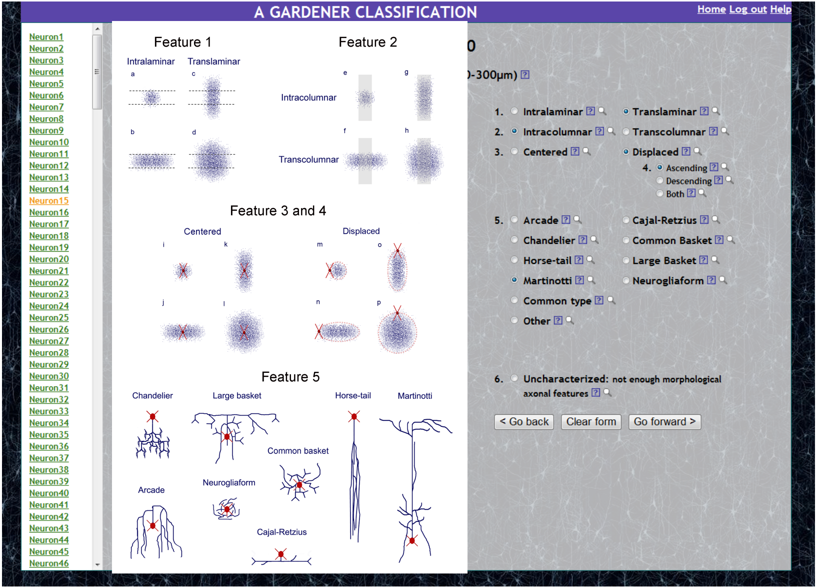
- A ‘gardener’ approach (not a botanist), coarser and practical
- Towards a consensus in naming GABAergic cortical interneurons
  - 10-30% of the total neuron population and main component of inhibitory cortical circuits
  - Located in all cortical layers and with a great variety of morphological, biochemical, and physiological characteristics
- Goal: a community-based strategy for defining a morphological taxonomy, establishing a list of terms to be used by all researchers to distinguish neuronal morphologies

DeFelipe, López-Cruz, Benavides-Piccione, Bielza, Larrañaga, *et al.* (2013). New insights into the classification and nomenclature of cortical GABAergic interneurons, ***Nature Reviews Neuroscience***, 14, 202-216

Collecting the data: 320 interneurons, 42 experts



Collecting the data: 320 interneurons, 42 experts



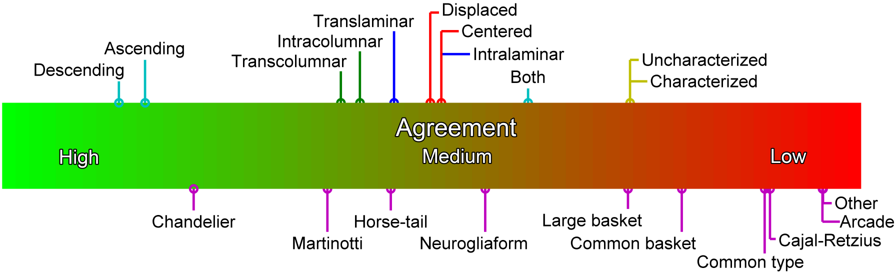
Data

Neuron		Feature 1	
	E_1	···	E_{42}
1	1	···	0
2	0	···	0
···		···	
320	0	···	0

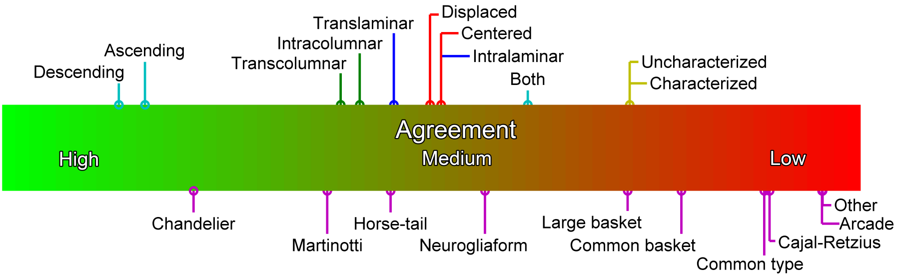
Data

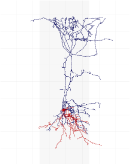
	Feature 1				Feature 5			Feature 6		
Neuron	E_1	···	E_{42}		E_1	···	E_{42}	E_1	···	E_{42}
1	1	···	0		5	···	8	0	···	1
2	0	···	0	······················	5	···	10	1	···	1
···		···				···			···	
320	0	···	0		1	···	4	1	···	0

Inter-expert agreement

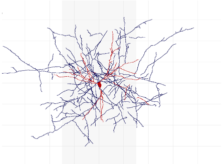


Inter-expert agreement





Martinotti (41)



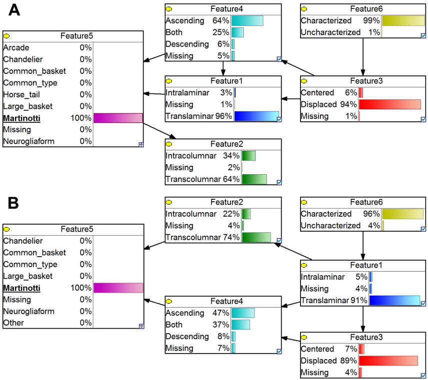
Large basket (15), Common type (12), Common basket (12), Arcade (3)

Supervised classification of each feature

2,886 morphological predictors, 240 neurons

	NB	NBdisc	RBFN	SMO	IB1	IB3	JRip	J48	RForest	RTree
Feature 1: Intralaminar vs. Translaminar										
NoFSS	57.68	58.51	77.59	82.16*	72.2	73.44	82.57*	**85.48***	82.16*	75.93
Gain Ratio	64.73	54.36	79.67	82.99*	69.71	75.93	83.82*	**85.48***	84.23*	79.67
CfsSubset	75.93	75.1	81.33	84.23*	73.86	80.08	**84.65***	80.08	82.16*	80.08
Feature 2: Intracolumnar vs. Transcolumnar										
NoFSS	59.75*	62.66*	52.28	**75.52***	57.68*	65.56*	74.27*	68.46*	66.39*	58.09*
Gain Ratio	66.39*	63.07*	53.11	**76.35***	64.32*	65.98*	75.52*	68.88*	70.12*	65.98*
CfsSubset	72.61*	65.56*	76.76*	**81.33***	73.86*	73.03*	74.69*	70.54*	76.35*	69.29*
Feature 3: Centered vs. Displaced										
NoFSS	62.24	53.94	54.77	**68.88***	64.73*	68.05*	66.8*	67.63*	68.46*	62.24
Gain Ratio	64.73*	**73.03***	65.98*	70.54*	65.56*	71.37*	70.54*	66.39*	72.2*	68.46*
CfsSubset	68.88*	**73.86***	70.54*	73.03*	65.15*	68.05*	63.9*	71.78*	68.46*	65.15*
Feature 4: Ascending vs. Descending vs. Both										
NoFSS	34.44	27.8	44.4*	49.38*	41.91	38.59	33.61	**54.36***	40.25	37.76
Gain Ratio	43.57*	33.2	43.98*	**49.79***	41.91	42.32	43.57*	46.89*	45.64*	42.74
CfsSubset	47.3*	51.87*	47.3*	58.51*	47.3*	52.28*	48.13*	42.32	**60.17***	47.3*
Feature 5: Interneuron type (10 classes)										
NoFSS	56.02*	19.09	45.23*	**58.51***	50.62*	53.94*	50.62*	47.72*	52.28*	40.25*
Gain Ratio	60.17*	26.14	58.92*	**62.24***	49.79*	51.87*	48.55*	43.15*	58.09*	43.98*
CfsSubset	61*	43.57*	**61.41***	60.58*	58.09*	56.85*	53.94*	49.38*	56.85*	51.45*
Feature 6: Characterized vs. Uncharacterized										
NoFSS	77.18	88.38	95.85	**97.93***	97.51	97.51	**97.93***	97.51	96.27	95.85
Gain Ratio	**98.34***	73.86	97.51	96.68	97.1	97.51	97.93*	97.93*	97.51	**98.34***
CfsSubset	97.51	89.63	96.27	97.1	95.44	95.02	97.93*	96.27	97.51	**99.17***

A Bayesian network learned for each expert



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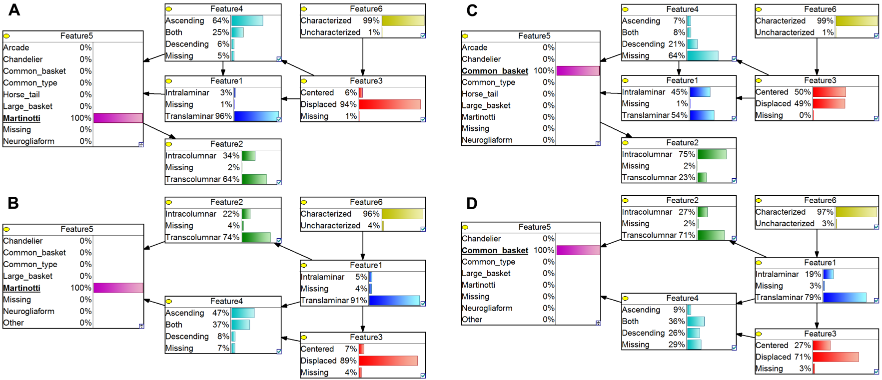
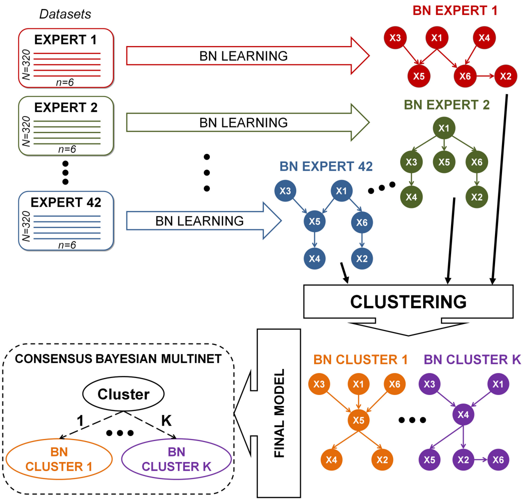


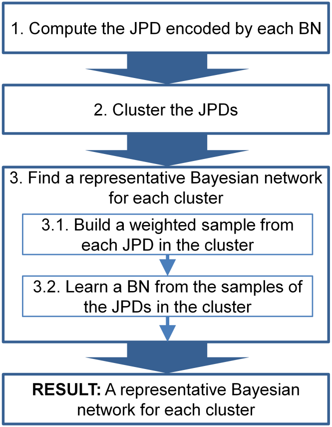
Outline

Inducing a consensus Bayesian multinet from a set of expert opinions



López-Cruz, Larrañaga, DeFelipe, Bielza (2014). Bayesian network modeling of the consensus between experts: An application to neuron classification, ***International J. of Approximate Reasoning***, 55, 3-22

Clustering of BNs encoding similar expert opinions



Clustering of BNs encoding similar expert opinions

1. Compute the JPD encoded by each BN

2. Cluster the JPDs

3. Find a representative Bayesian network for each cluster

3.1. Build a weighted sample from each JPD in the cluster

3.2. Learn a BN from the samples of the JPDs in the cluster

RESULT: A representative Bayesian network for each cluster

Steps 1 and 2

- Dataset with 42 JPDs $\times$ 121 values
- K-means algorithm ($K = 6$)
- Jensen-Shanon divergence as dissimilarity measure for JPDs

$$d_{JS}(\mathbf{p}_1, \mathbf{p}_2) = 0.5\,(KL(\mathbf{p}_1||\mathbf{m}) + KL(\mathbf{p}_2||\mathbf{m}))$$

where $\mathbf{m} = 0.5(\mathbf{p}_1 + \mathbf{p}_2)$

- Compute the cluster center $\bar{\mathbf{p}}_k$ from a set $\{\mathbf{p}_1, \ldots, \mathbf{p}_{N_k}\}$ in cluster k using LOGARITHMIC COMBINATION POOL:

$$\bar{p}_{jLogOp} = \frac{\prod_{i=1}^{N_k} p_{ij}^{\omega_i}}{\sum_{v=1}^{121} \prod_{i=1}^{N_k} p_{iv}^{\omega_i}}$$

with $\omega_i = 1/N_k$

Clustering of BNs encoding similar expert opinions

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RESULT: A representative Bayesian network for each cluster

Step 3

- For each cluster, sample from its JPDs. Draw $\mu_i \times M$ observations from each $\mathbf{p}_i$ in cluster k, where
$$\mu_i = \frac{1 - d_{JS}(\mathbf{p}_i, \overline{\mathbf{p}}_k)}{\sum_{j=1}^{N_k} \left(1 - d_{JS}(\mathbf{p}_j, \overline{\mathbf{p}}_k)\right)}$$
(degree of membership for $\mathbf{p}_i$ to cluster k)
- Learn a (representative) BN from the sample of size M

Cluster labeling (with marginals)

Cluster	# experts
1	3
2	15
3	4
4	12
5	7
6	1

Cluster labeling (with marginals)

Cluster	# experts
1	3
2	15
3	4
4	12
5	7
6	1

Cluster 3

Fine-grained classification scheme, trying to distinguish between the different neuronal types

Cluster labeling (with marginals)

Cluster	# experts
1	3
2	15
3	4
4	12
5	7
6	1

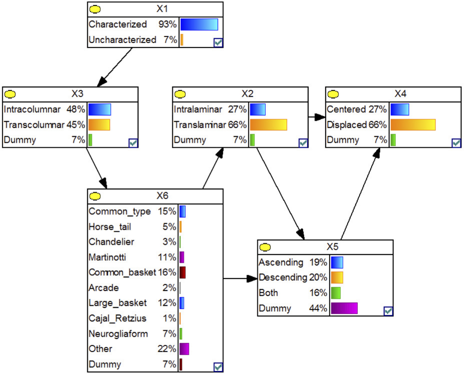
Cluster 4

Coarse classification scheme. High P to *Common type*

Cluster labeling (with marginals)

Cluster	# experts
1	3
2	15
3	4
4	12
5	7
6	1

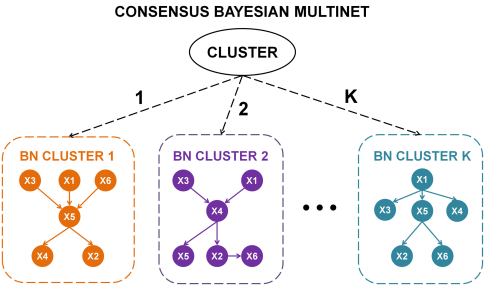
Cluster 5



Detailed classification scheme, distinguishing between *Common type*, *Common basket* and *Large basket*. Found the nomenclature incomplete (high P to *Other*)

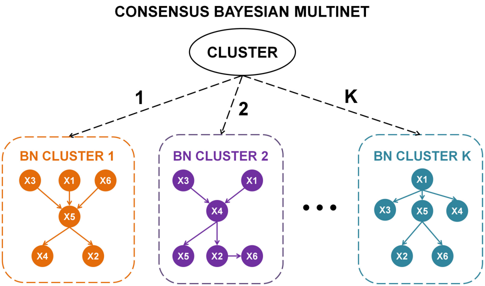
Final consensus Bayesian multinet representing all the experts

- Finite mixture of Bayesian networks: $P(\mathbf{X} = \mathbf{x}) = \sum_{k=1}^{K} \pi_k P_k(\mathbf{X} = \mathbf{x}|C = k)$ with $\pi_k = \frac{N_k}{42}$, P_k=representative BN



Final consensus Bayesian multinet representing all the experts

- Finite mixture of Bayesian networks: $P(\mathbf{X} = \mathbf{x}) = \sum_{k=1}^{K} \pi_k P_k(\mathbf{X} = \mathbf{x} | C = k)$ with $\pi_k = \frac{N_k}{42}$, P_k=representative BN



- Set evidence in X_6 to infer agreed definitions for neuron types:
  - *Martinotti*: Translaminar ($= .93$), Displaced ($= .88$), Ascending ($= .64$)
  - *Common type*: Translaminar ($= .71$)
- Etc.

Outline

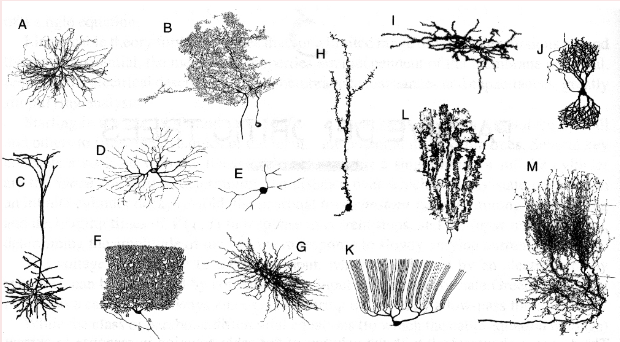
Computer simulation of dendritic morphology

Why so different dendritic tree shapes?

Computer simulation of dendritic morphology

Dendritic morphology

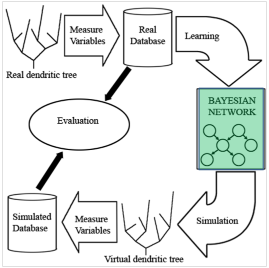
- Tree shapes → interconnectivity and functional roles of neurons
- Their normal function, in neurological diseases, under the effects of some drugs



- Typically grouped based on prominent geometrical features. Difficult to find 2 neurons with the same morphology → but branching patterns

⇒ Anatomical characterization is statistical in nature

Our proposal: advantages



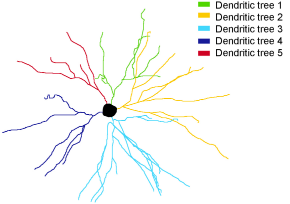
...with Bayesian networks

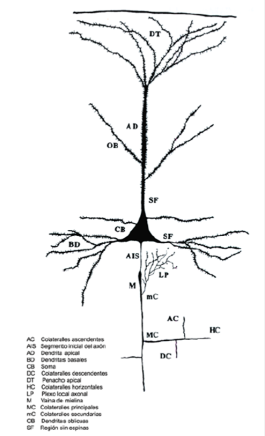
- (In)dependences between morphological properties automatically found from real data (vs. *prior conditional relationships ad hoc*)
- Model the joint probability distribution of all variables (vs. $\leq$ *trivariate* and *standard distributions*)
- Reliable evaluation: statistical tests to compare original vs. simulated distributions, both uni and multivariate (vs. *on new 1D pars and visual inspection*)

López-Cruz, Bielza, Larrañaga, Benavides-Piccione, DeFelipe (2011). Models and simulation of 3D neuronal dendritic trees using Bayesian networks, ***Neuroinformatics***, 9, 347-369

Data: pyramidal neurons

- 3D reconstructions of 90 pyramidal neurons from the mouse neocortex, traced with *Neurolucida* package
- Layer III of different cortical regions: M2, S2, V2L/TeA
  $\Rightarrow$ 3 databases
- Each basal arbor with 6 (average) main trunks –dendritic trees–, each made up of several dendrites





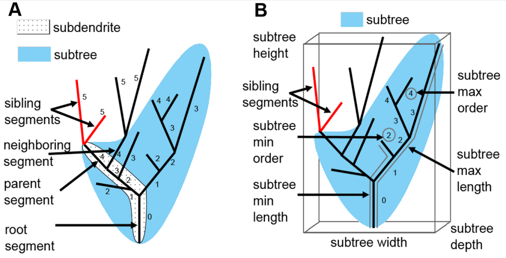
Cortex region	Database	# dendr. trees
Motor	M2	104
Somatosensory	S2	103
Lateral visual and association temporal	V2L/TeA	156

Publicly available at `http://neuromorpho.org` as part of DeFelipe's archive (same lab)

Features

Morphological parameters

- For each pair of sibling segments (line between two branch points), measure 41 variables
- Widely used and also new, to capture context influence and neuritic competition
- Evidence variables: measure the part of the tree previous to a pair of sibling segments (subtree and subdendrite involved). Measured during the simulation, used as information to sample construction variables
- Construction variables: define the morphology of a segment (segment length, orientation, bifurcation). Sample from them to incrementally construct trees



List of variables

No.	Type	Variable	No.	Type	Variable
1	E	subtree degree (no. endings)	22	E	neighbor distance
2	E	subtree no. bifurcations (no. nodes)	23	E	neighbor inclination
3	E	subtree total length	24	E	neighbor azimuth
4	E	subtree width	25	E	neighbor extension
5	E	subtree height	26	E	neighbor angle
6	E	subtree depth	27	E	parent segment length
7	E	subtree box volume	28	E	parent segment inclination
8	E	subtree max distance between nodes	29	E	parent segment azimuth
9	E	subtree max distance to soma	30	E	root segment length
10	E	subtree max length	31	E	root segment inclination
11	E	subtree min length	32	E	root segment azimuth
12	E	subtree max order	33	E	segment centrifugal order
13	E	subtree min order	34	C	left segment length
14	E	subdendrite length	35	C	left segment inclination
15	E	subdendrite width	36	C	left segment azimuth
16	E	subdendrite height	37	C	left segment bifurcates
17	E	subdendrite depth	38	C	right segment length
18	E	subdendrite box volume	39	C	right segment inclination
19	E	subdendrite distance to soma	40	C	right segment azimuth
20	E	subdendrite inclination	41	C	right segment bifurcates
21	E	subdendrite azimuth			

Variables **discretized** (2-3 values) trying to preserve empirical distributions

Bayesian network learning

Overview of the learning

- Learn and use a BN for each part of the dendritic tree, to allow specific relationships at each part

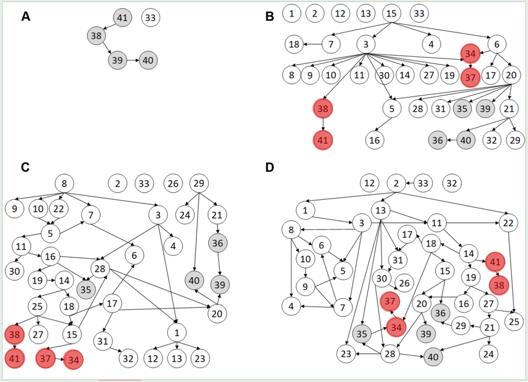
- $P(X_1, ..., X_{41}) = \prod_{i=1}^{n=41} P(X_i|\Pi_i)$ $\quad\quad$ Π_i = parents of X_i in the graph
- Learn the structure via BIC score and K2 heuristic search
  - MWST algorithm for having an ordering between nodes (weight=BIC)
  - Force evidence variables *before* construction variables
  - Fix an upper bound on the max number of parents for any node *(=3)*
- Learn the parameters (probabilities) via MLE

$$P(X_i = x_i|\Pi_i = \pi_i) = \frac{freq(X_i = x_i, \Pi_i = \pi_i)}{freq(\Pi_i = \pi_i)}$$

Bayesian networks learned

For M2 database

- A, B, C, D $\rightarrow$ root segments, order 1, order 2, $>$ 2 order, resp. Shaded = construction variables

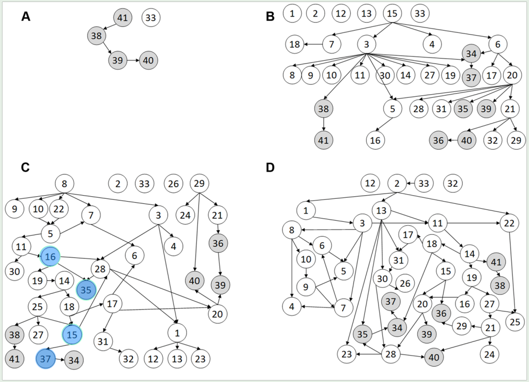


- Found relationships conform to biological knowledge, e.g.
  Segment length (34, 38) and bifurcation (37, 41) occurrence $\rightarrow$ more bifurcations close to the soma and shorter segments, whereas segments that do not branch spread away from the soma

Bayesian networks learned

For M2 database

- A, B, C, D → root segments, order 1, order 2, > 2 order, resp. Shaded = construction variables

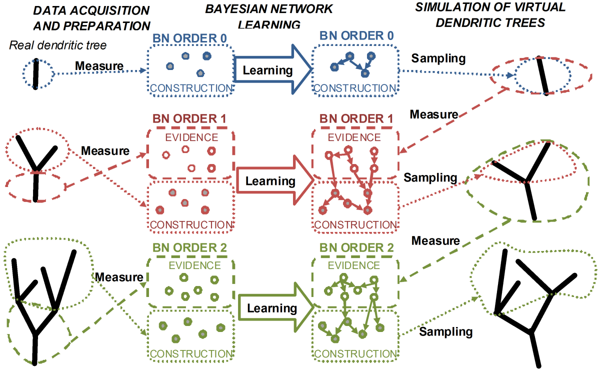


- Found relationships conform to biological knowledge, e.g.
  Subdendrite width (15) and segment bifurcation (37) [wider → doesn't bifurcate] → constrain tree size.
  Smaller inclination angles (35) for taller subdendrites (16), etc

Simulation of virtual dendritic trees

Procedure (breadth-first way)

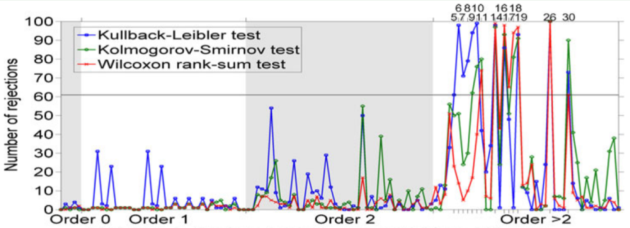
1. Generate a root segment
2. Measure evidence variables from the dendritic tree built so far
3. Sample construction variable values from the Bayesian network
4. If a segment bifurcates, consider that the dendrite is still incomplete and go to 2. Else, the dendrite has ended



Model validation

Compare real/simulated prob. distributions

- Simulate the same number of dendritic trees than in the original database
- Univariate statistical tests (compare marginal distributions): KS, Wilcoxon rank-sum, KL (with `bioDist` R package to estimate KL for continuous variables, and bootstrap to estimate percentile 95)
- Repeat 100 times to consider statistical variability and perform a sign test for each test to check if the number of rejections was significant in the 100 repetitions



M2 area

- Some rejections in evidence variables in higher orders (high variability)
- No rejections for construction vars

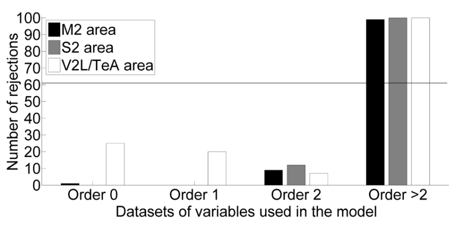
Model validation

Compare real/simulated prob. distributions

- Multivariate statistical test (compare the joint distribution), used for the first time in this context
- ...Use multivariate KL estimator based on k-NN density estimation [Wang et al., 2006]

$$\widehat{KL}(p||q) = \frac{n}{N_p} \sum_{i=1}^{N_p} \log \frac{\upsilon_{D_q}(i)}{\rho_{D_p}(i)} + \log \frac{N_q}{N_p - 1}$$

Datasets D_p, D_q with n-dim samples of sizes N_p, N_q,
$\rho_{D_p}(i)$=distance from $\mathbf{x}_i \in D_p$ to its NN in D_p, $\upsilon_{D_q}(i)$=distance to its NN in D_q

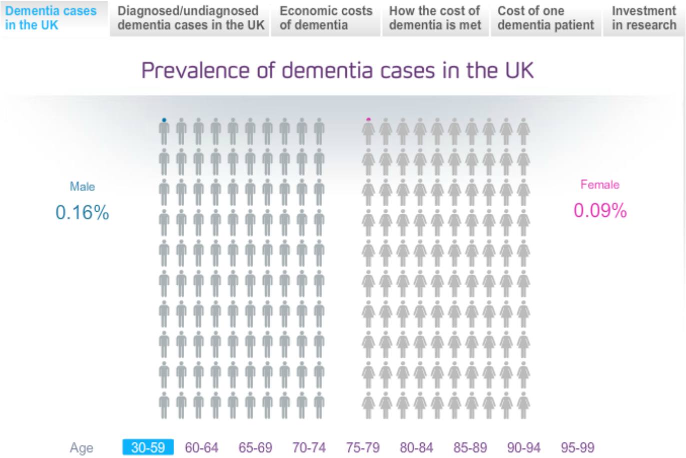


- Worse for higher orders (high variability) –perhaps due to the previous variables

Outline

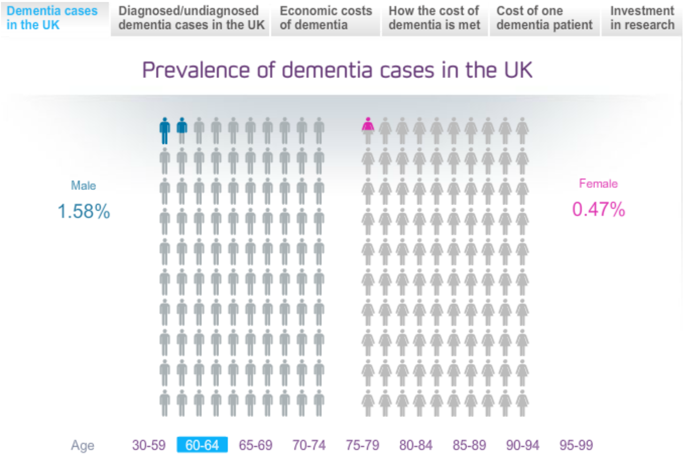
Outline

Dementia: Prevalence, cost and investment in research



http://www.alzheimersresearchuk.org/dementia-statistics/

Dementia: Prevalence, cost and investment in research



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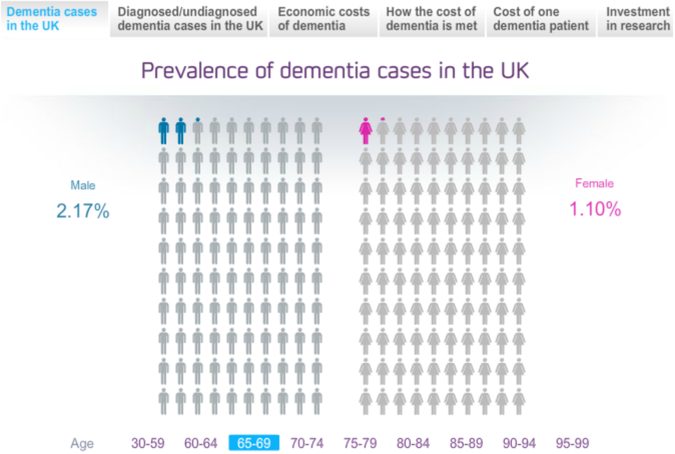

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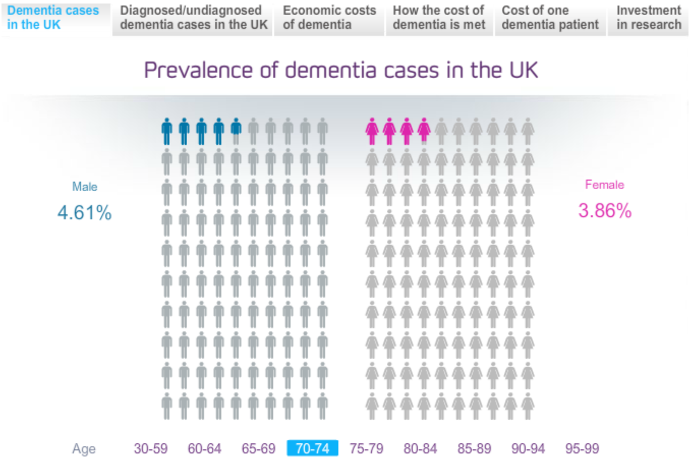

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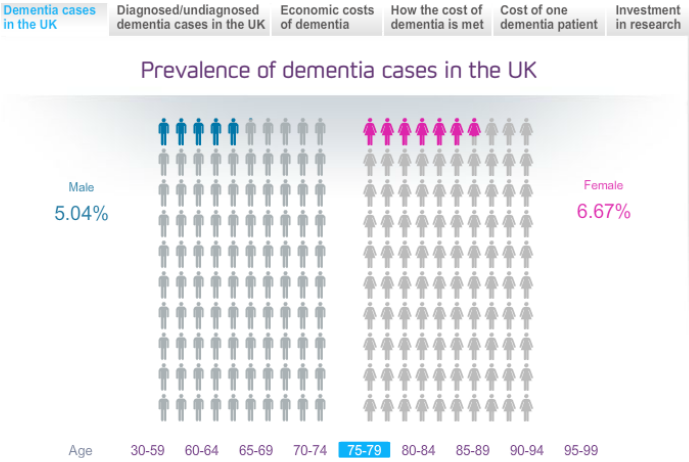

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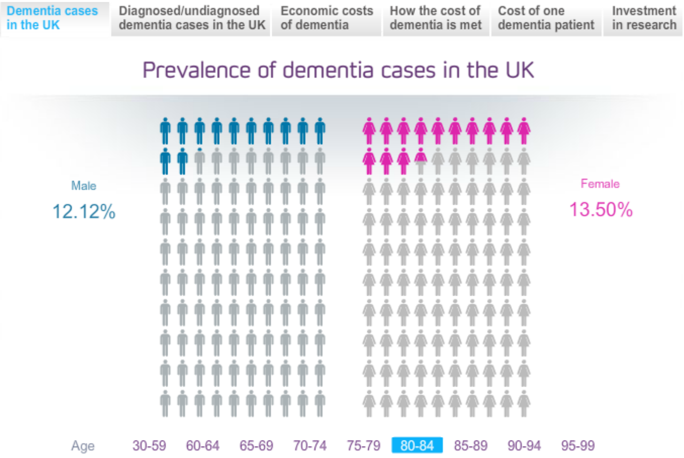

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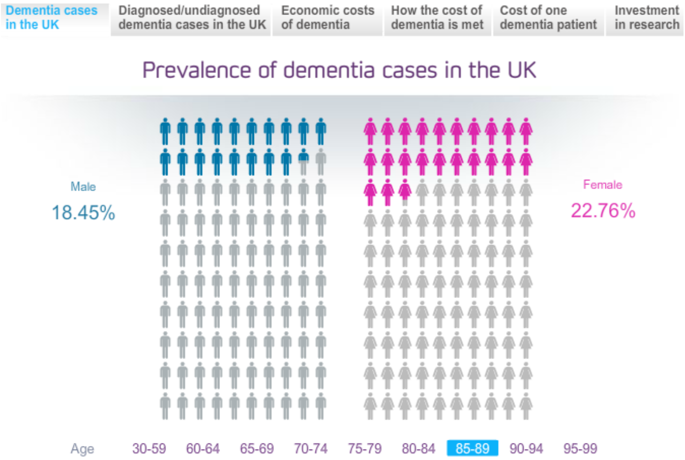

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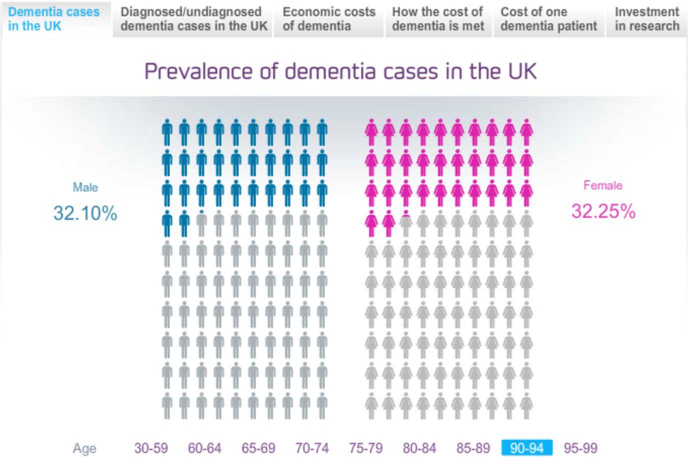

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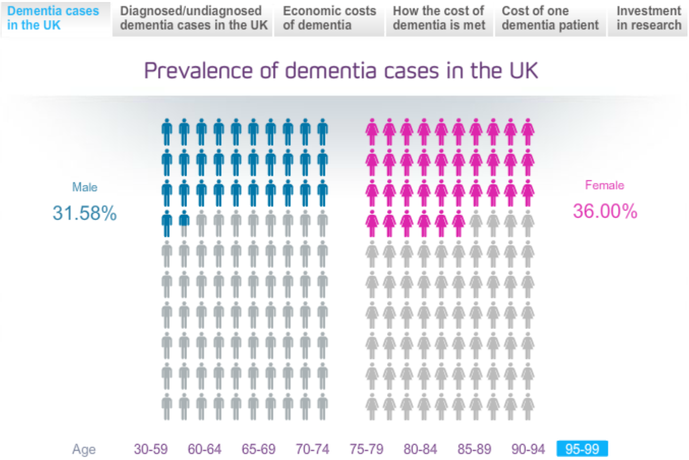

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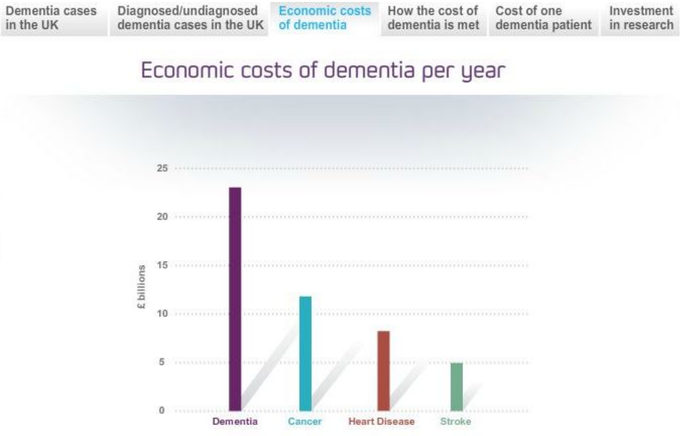

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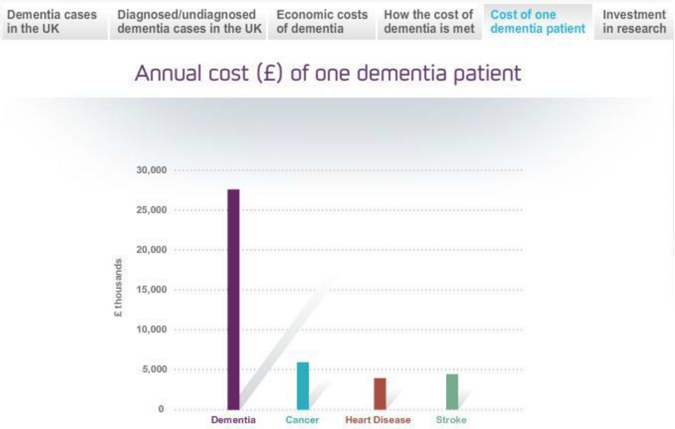

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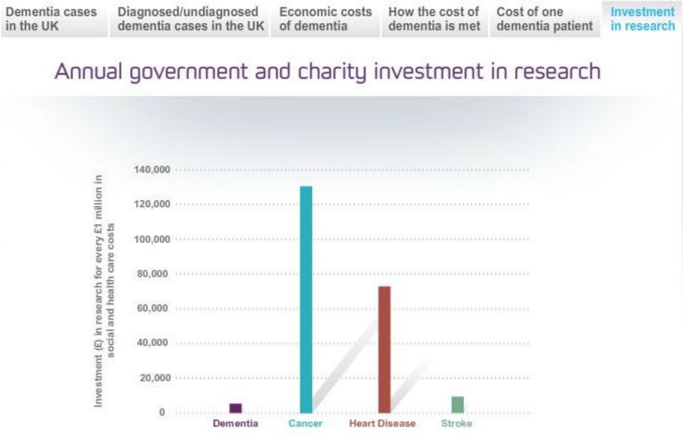

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Outline

1. Introduction
2. Neuroanatomy: neurons and dendritic trees
   - 'Gardener' classification of neurons
   - Bayesian networks to model consensus among experts
   - Computer simulation of dendritic morphology
3. Neurology: Parkinson and Alzheimer
   - Dementia: Prevalence, cost and investment in research
   - Knowledge discovery in Alzheimer's disease
   - Multi-dimensional classification for EQ-5D from PDQ-39 in Parkinson's disease
4. Conclusions

Knowledge discovery in Alzheimer's disease

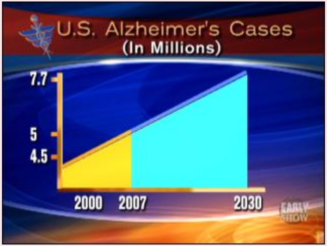
Can we discover knowledge in AD from microarray data with a few brains?

Knowledge discovery in Alzheimer's disease

Alzheimer's disease

- Primarily affects the elderly and manifests through memory disorders, cognitive decline and loss of autonomy

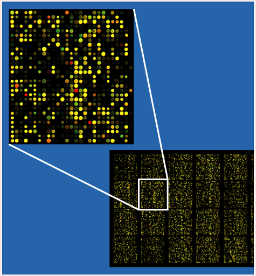
Alois Alzheimer (1864-1915)

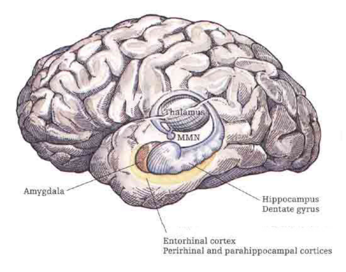


- In 2014, 44 million cases worldwide (7.2 in Europe). By 2050, rates could exceed 135 million
- Every 4 seconds, a new case of dementia occurs somewhere
- Sixth-leading cause of death in USA

Knowledge discovery in Alzheimer's disease

Alzheimer's disease and DNA microarrays





- Idea in [Small et al., 2005]: microarray data selectively from the brain site most
  - vulnerable to AD to maximize expression differences between AD and controls: entorhinal cortex (EC)
- 6 AD brains + 6 control brains ⇒ 12 tissue samples and 7,610 variables

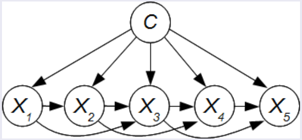
Small et al. (2005). Model-guided microarray implicates the retromer complex in Alzheimer's disease, *Annals of Neurology*, 58(6), 909-919

Knowledge discovery in Alzheimer's disease

- ⇒ Re-analyze the data differently to gain robustness (small sample size!)
- ⇒ Find out explicit new (or validate old) biological relationships and genes not previously reported

Reliable-kDB classifier with robust gene interactions

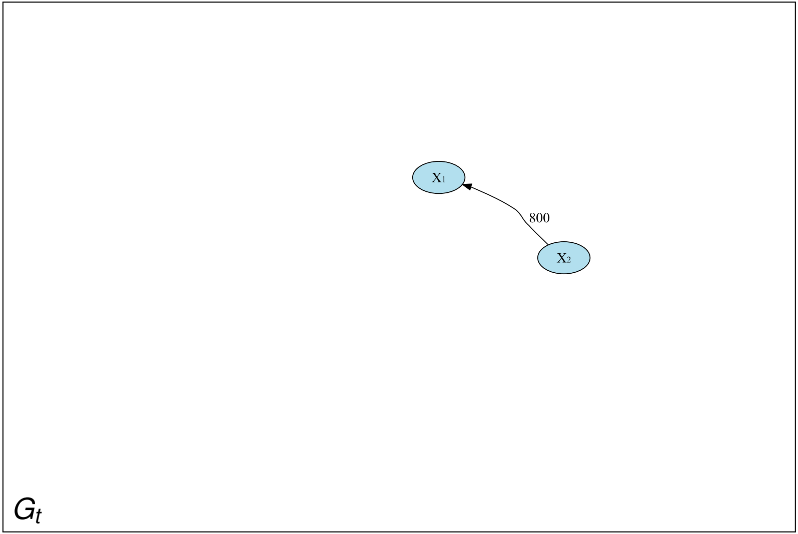
- Learn a Bayesian network classifier. We use kDB structures with at most k parents (excluding the class)



- Induce many kDB by a resampling method (bootstrap) with an inner FSS
- Output a network with those arcs above a reliability threshold t: arcs occurring $\geq t$ times are retained
- Approach is a consensus feature selection on the final gene interaction network

Armañanzas, Larrañaga, Bielza (2012). Ensemble transcript interaction networks: A case study on Alzheimer's disease, ***Computer Methods and Programs in Biomedicine***, 108, 442-450

Reliable-kDB classifier –An example



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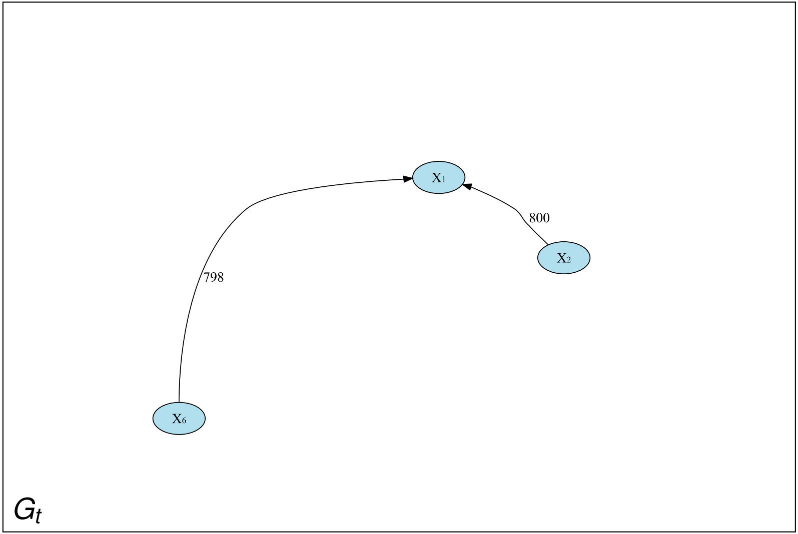
Reliable-kDB classifier –An example



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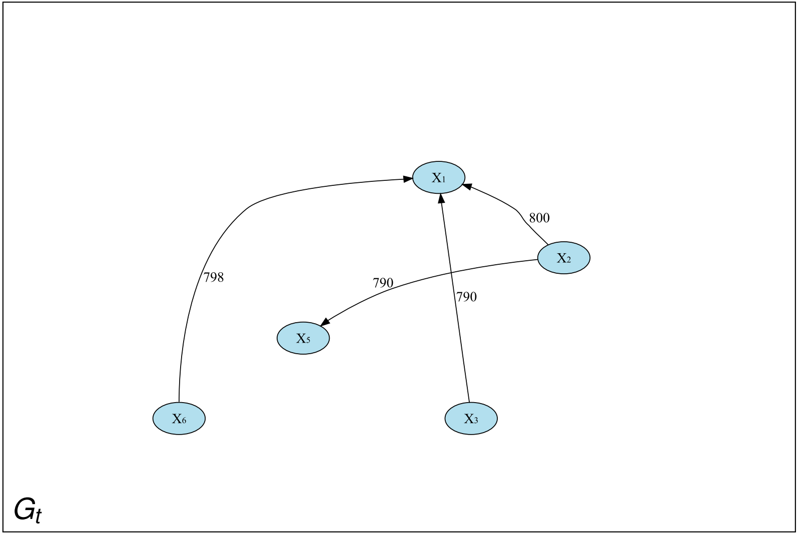

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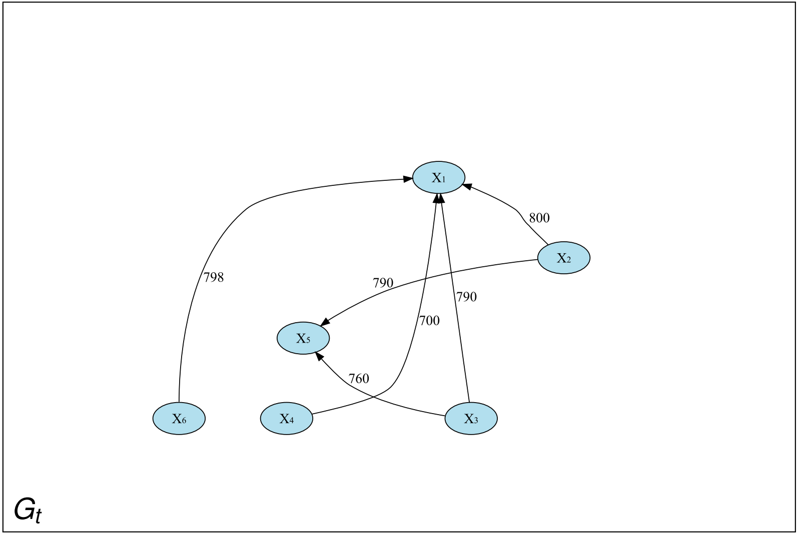

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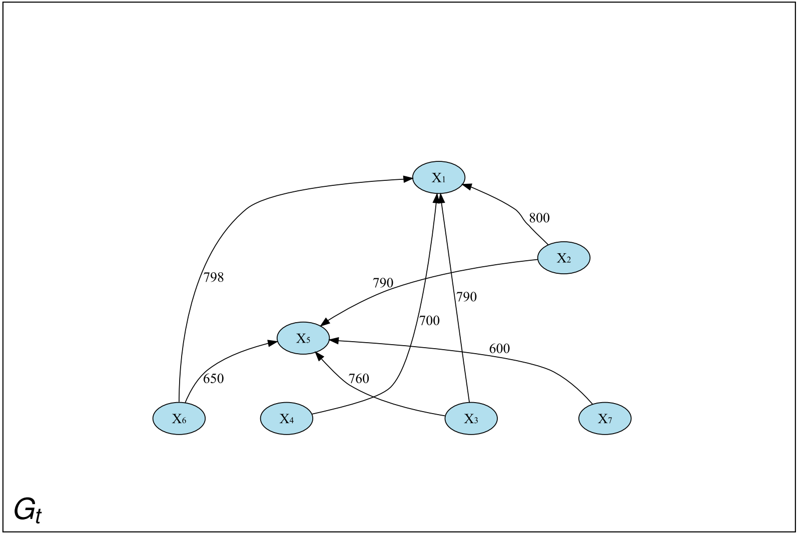

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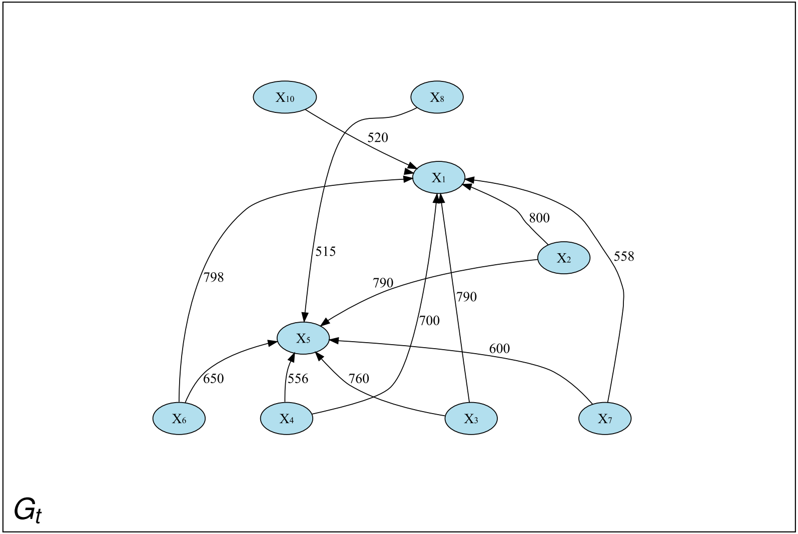

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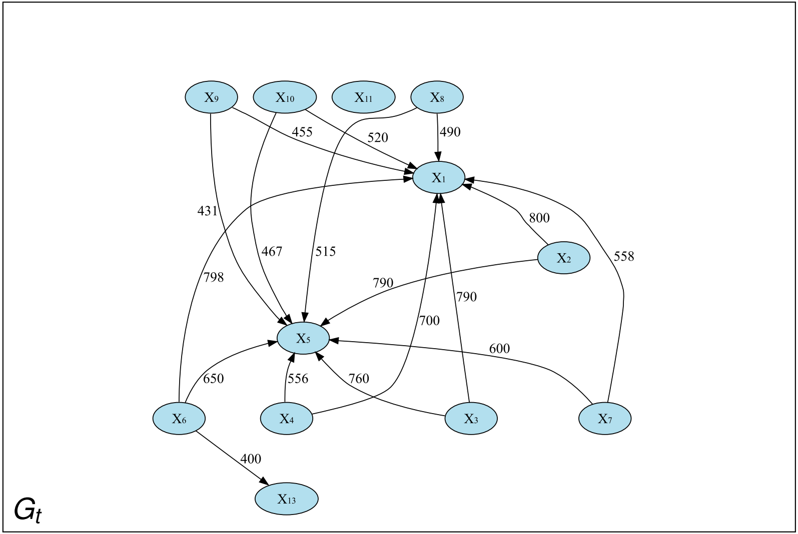

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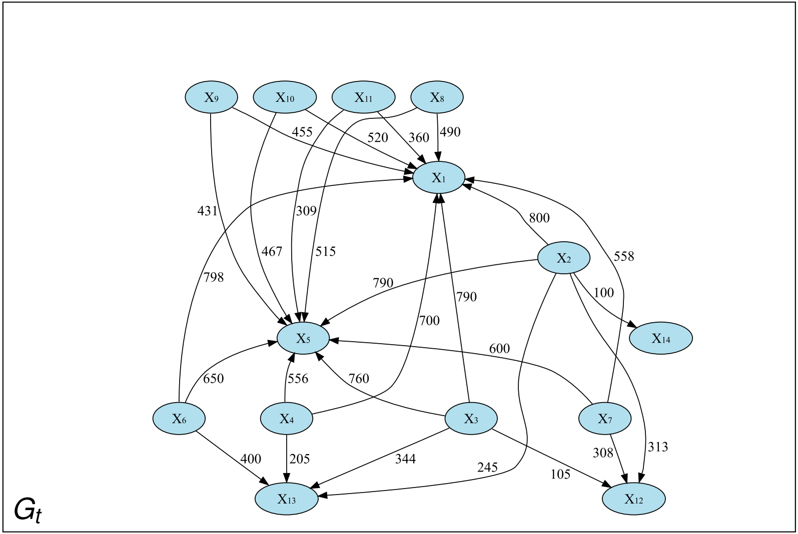

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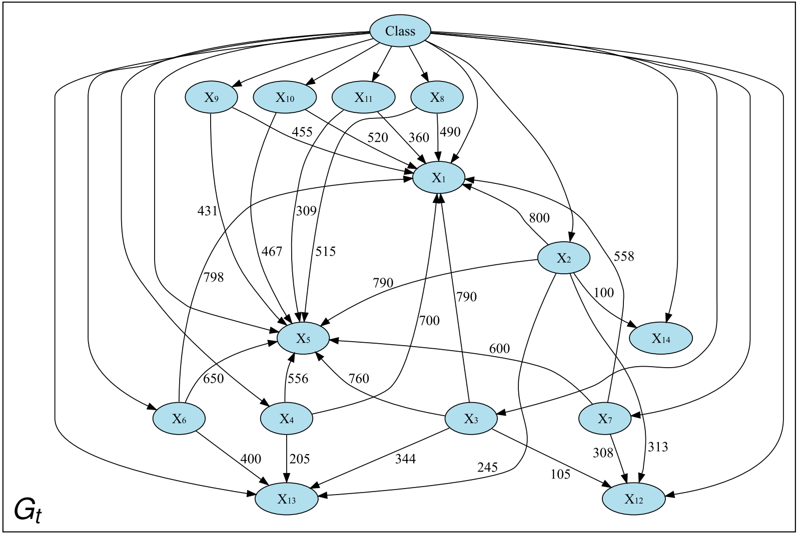

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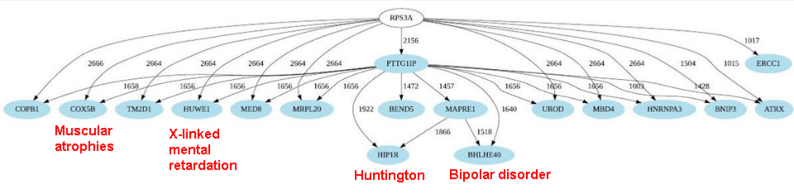
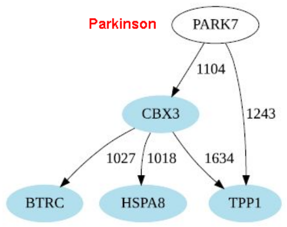
Knowledge discovery in Alzheimer's disease

AD vs. Controls (12 samples) with $k = 4$, $B = 10000$, $t = 1000$





Outline

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

Is it possible to map from PD patient's perception PDQ-39 to the general health scale EQ-5D?

PDQ-39 and EQ-5D

PDQ-39 and EQ-5D: quality of life instruments to measure the degree of disability in PD

39-item Parkinson's Disease Questionnaire: a specific instrument

PDQ-39 captures patient's perception of his illness covering 8 dimensions:

1. Mobility
2. Activities of daily living
3. Emotional well-being
4. Stigma
5. Social support
6. Cognitions
7. Communication
8. Bodily discomfort

PDMED

PDQ-39 QUESTIONNAIRE

Please complete the following

Please tick one box for each question

Due to having Parkinson's disease, how often during the last month have you....		Never	Occasionally	Sometimes	Often	Always or cannot do at all
1	Had difficulty doing the leisure activities which you would like to do?	☐	☐	☐	☐	☐
2	Had difficulty looking after your home, e.g. DIY, housework, cooking?	☐	☐	☐	☐	☐
3	Had difficulty carrying bags of shopping?	☐	☐	☐	☐	☐
4	Had problems walking half a mile?	☐	☐	☐	☐	☐
5	Had problems walking 100 yards?	☐	☐	☐	☐	☐
6	Had problems getting around the house as easily as you would like?	☐	☐	☐	☐	☐

PDQ-39 and EQ-5D

European Quality of Life - 5 Dimensions: a generic instrument

EQ-5D is a generic measure of health for clinical and economic appraisal

Mobility
I have no problems in walking about
I have some problems in walking about
I am confined to bed

Self-care
I have no problems with self-care
I have some problems washing and dressing myself
I am unable to wash and dress myself

Usual activities (eg. work, study, housework, family or leisure activities)
I have no problems with performing my usual activities
I have some problems with performing my usual activities
I am unable to perform my usual activities

Pain/discomfort
I have no pain or discomfort
I have moderate pain or discomfort
I have extreme pain or discomfort

Anxiety/depression
I am not anxious or depressed
I am moderately anxious or depressed
I am extremely anxious or depressed

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

Mapping PDQ-39 to EQ-5D

PDQ_1	PDQ_2	...	...	PDQ_{39}	EQ_1	EQ_2	EQ_3	EQ_4	EQ_5
3	1	...	...	3	1	3	3	2	1
2	3	...	...	2	1	1	2	3	2
5	2	...	...	4	1	3	3	1	2
...	...	...	...	...	...	...	...	...	...
4	4	...	...	3	3	1	2	3	2
4	4	...	...	3	3	1	2	3	2
5	5	...	...	4	2	3	2	3	3

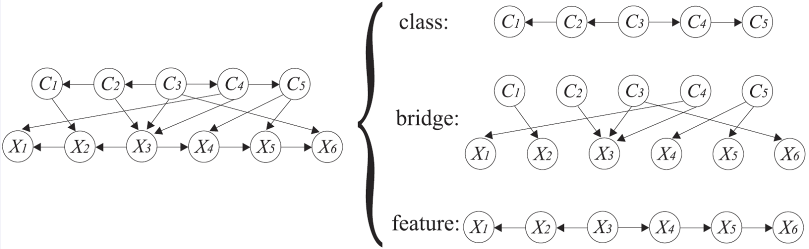
$$h : (PDQ_1, ..., PDQ_{39}) \rightarrow (EQ_1, ..., EQ_5)$$

Borchani, Bielza, Martínez-Martín, Larrañaga (2012). Multidimensional Bayesian network classifiers applied to predict the European quality of life-5 dimensions (EQ-5D) from the 39-item Parkinson's disease questionnaire (PDQ-39), ***Journal of Biomedical Informatics***, 45, 1175-1184

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

Multi-dimensional Bayesian network classifier (MBC)

- The set of variables $\mathcal{V}$ is partitioned into:
  - $\mathcal{V}_\mathcal{C} = \{C_1, \ldots, C_d\}$ of class variables and
  - $\mathcal{V}_\mathcal{X} = \{X_1, \ldots, X_m\}$ of feature variables



Most probable explanation (MPE)

$$(c_1^*, \ldots, c_d^*) = \max_{c_1,\ldots,c_d} p(C_1 = c_1, \ldots, C_d = c_d | X_1 = x_1, \ldots, X_m = x_m)$$

Bielza, Li, Larrañaga (2011). Multi-dimensional classification with Bayesian networks, ***International Journal of Approximate Reasoning***, 52(6), 705-727

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

Four MBC learning algorithms

1. Markov blanket – Multi-dimensional Bayesian classifier (MB–MBC) [Borchani et al., 2011]

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

Four MBC learning algorithms

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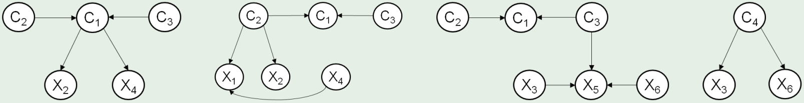

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

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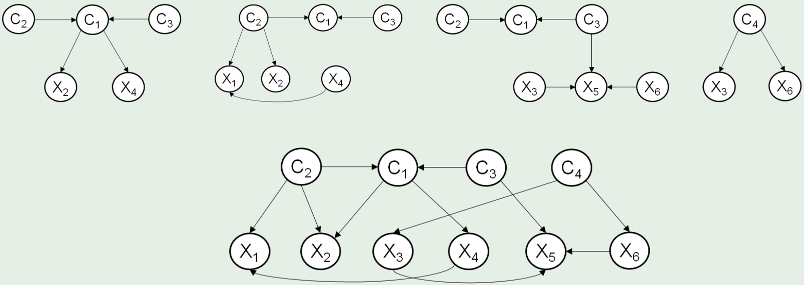

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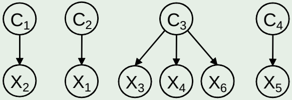

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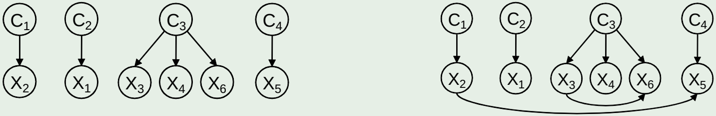

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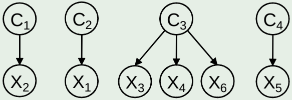

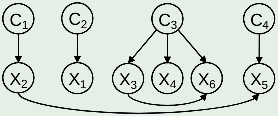

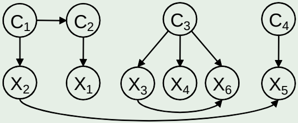

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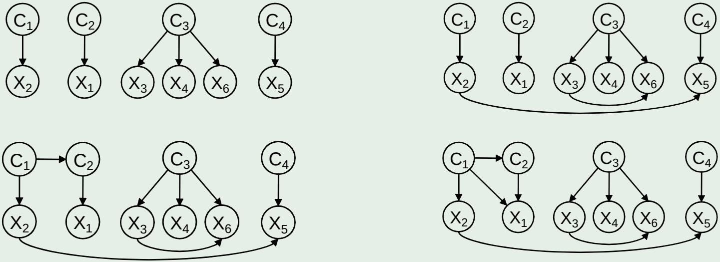

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4. Independent Markov blanket classifiers with PC algorithm (Indep-MB-PC) [Le and Doctor, 2011]

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- Borchani, Bielza, Larrañaga (2011). *Probabilistic Problem Solving in Biomedicine. Workshop in the 13th Conference on Artificial Intelligence in Medicine*, 29-40
- Borchani, Bielza, Larrañaga (2010). *Proc. of the 5th Workshop on Probabilistic Graphical Models*, 25-32
- Aliferis et al. (2010). *Journal of Machine Learning Research*, 11, 235-284
- Le and Doctor (2011). *Medical Care*, 49(5), 451-460

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

488 Parkinson's patients. Estimated measures over 5-fold cross-validation

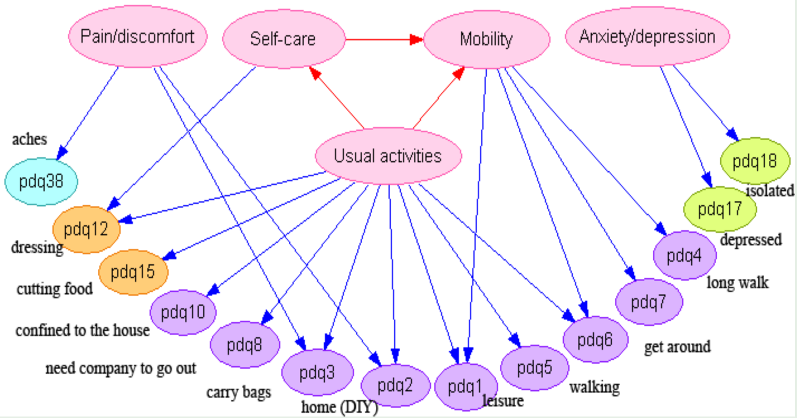
Method	Mean accuracy	Global accuracy	MSE
`MB-MBC`	**0.7119 ± 0.0338**	0.2030 ± 0.0718	**0.0650 ± 0.0156**
`CB-MBC`	0.6807 ± 0.0285	0.1865 ± 0.0429	0.0905 ± 0.0167
`Indep-MB-HITON`	0.7009 ± 0.0427	**0.2051 ± 0.0835**	0.0699 ± 0.0188
`Indep-MB-PC`	0.6587 ± 0.0636	0.1867 ± 0.0937	0.0909 ± 0.0909
`MNL`	0.6926 ± 0.0430	0.1802 ± 0.0713	0.0759 ± 0.0152
`OLS`	0.4201 ± 0.0252	0.0123 ± 0.0046	0.1832 ± 0.0373
`CLAD`	0.4254 ± 0.0488	0.0143 ± 0.0171	0.1962 ± 0.0360

$d = 5, N = 488$

- Mean accuracy over the d class variables: $Acc_m = \frac{1}{d}\sum_{i=1}^{d}\frac{1}{N}\sum_{l=1}^{N}\delta(\hat{c}_{li}, c_{li})$
- Global accuracy over the d-dimensional class variable: $Acc_g = \frac{1}{N}\sum_{l=1}^{N}\delta(\hat{\mathbf{c}}_l, \mathbf{c}_l)$
- MSE between the true and predicted EQ-5D utility scores

Multi-dimensional classification for EQ-5D health states from PDQ-39 in Parkinson

MB–MBC graphical structure



Outline

1. Introduction
2. Neuroanatomy: neurons and dendritic trees
   - ‘Gardener’ classification of neurons
   - Bayesian networks to model consensus among experts
   - Computer simulation of dendritic morphology
3. Neurology: Parkinson and Alzheimer
   - Dementia: Prevalence, cost and investment in research
   - Knowledge discovery in Alzheimer’s disease
   - Multi-dimensional classification for EQ-5D from PDQ-39 in Parkinson’s disease
4. **Conclusions**

Neuroscience and Bayesian networks

Challenging machine learning problems in modeling the brain

- JOINT PROBABILITY DISTRIBUTION: Bayesian networks (classifying neuron types, dendritic morphology)
- CONSENSUS OF PROBABILISTIC MODELS: Bayesian networks and multinets (a neuroscientist $\equiv$ a model)
- BOOTSTRAP FOR RELIABLE MODELS: k-DB Bayesian classifiers (knowledge discovery in Alzheimer's disease)
- MULTI-DIMENSIONAL CLASSIFICATION: multi-dimensional Bayesian classifiers (from PDQ-39 to EQ-5D in Parkinson's disease)

Ongoing work

	Feature 1			Feature 5			Feature 6		
Neuron	E_1	...	E_{42}	E_1	...	E_{42}	E_1	...	E_{42}
1	1	...	0	5	...	8	0	...	1
2	0	...	0	5	...	10	1	...	1
...		...			...			...	
320	0	...	0	1	...	4	1	...	0

Ongoing work

Neuron	Feature 1 E_1	⋯	Feature 1 E_{42}	⋯	Feature 5 E_1	⋯	Feature 5 E_{42}	Feature 6 E_1	⋯	Feature 6 E_{42}
1	1	⋯	0		5	⋯	8	0	⋯	1
2	0	⋯	0	⋯⋯⋯⋯⋯⋯⋯⋯	5	⋯	10	1	⋯	1
⋯		⋯				⋯			⋯	
320	0	⋯	0		1	⋯	4	1	⋯	0

Neuron	X_1	X_2	⋯	X_{2886}	Count vector with votes: *Intralaminar* vs *Translaminar*	Probability distribution: *Intralaminar* vs *Translaminar*
1	8.4	7.1	⋯	2.1	(38, 4)	(.90,.10)
2	2.0	5.4	⋯	4.0	(3, 39)	(.07,.93)
3	7.3	2.0	⋯	1.1	(10,32)	(.24,.76)
⋯		⋯⋯⋯⋯			⋯	⋯
240	3.7	2.8	⋯	5.2	(24,18)	(.57,.43)

Bayesian classifiers for probabilistic class labels

Ongoing work

	Feature 1				Feature 5			Feature 6		
Neuron	E_1	...	E_{42}	....	E_1	...	E_{42}	E_1	...	E_{42}
1	1	...	0		5	...	8	0	...	1
2	0	...	0		5	...	10	1	...	1
...		...				...			...	
320	0	...	0		1	...	4	1	...	0

Ongoing work

	Feature 1				Feature 5			Feature 6		
Neuron	E_1	...	E_{42}		E_1	...	E_{42}	E_1	...	E_{42}
1	1	...	0		5	...	8	0	...	1
2	0	...	0	....	5	...	10	1	...	1
...		...				...			...	
320	0	...	0		1	...	4	1	...	0

	128 Axon, 86 Dendrite, 10 Soma				≥ 26 votes
Neuron	X_1	X_2	...	X_{224}	C
1	8.4	7.1	...	2.1	Martinotti (27)
2	2.0	5.4	...	4.0	?
3	7.3	2.0	...	1.1	?
...		....			...
240	3.7	2.8	...	5.2	Basket (32)

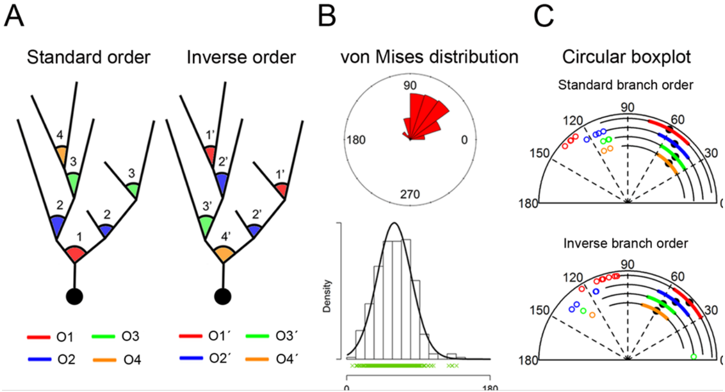
Semi-supervised classification/clustering

Ongoing work

	Feature 1				Feature 5			Feature 6		
Neuron	E_1	···	E_{42}		E_1	···	E_{42}	E_1	···	E_{42}
1	1	···	0		5	···	8	0	···	1
2	0	···	0	....	5	···	10	1	···	1
···		···				···			···	
320	0	···	0		1	···	4	1	···	0

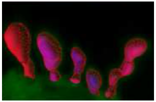
Multi-dimensional classification (data streams?)

Ongoing work

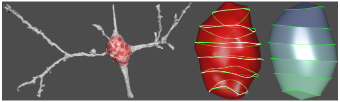


Bayesian networks with angular variables: association, classification

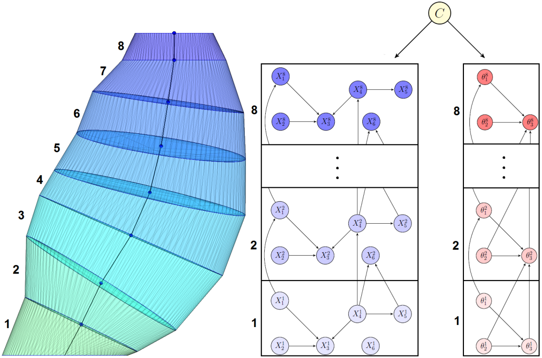
Ongoing work



Spines

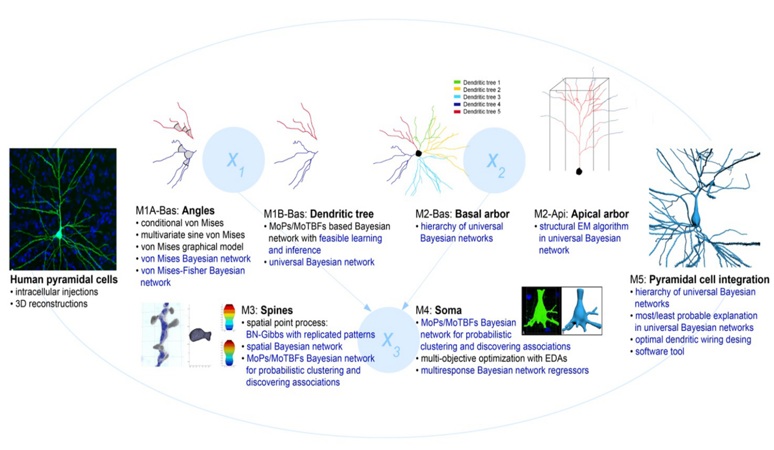


Soma



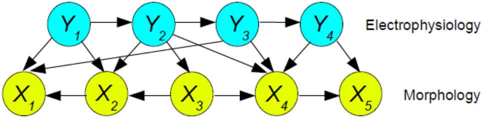
“Dynamic” Bayesian networks with continuous and angular variables: clustering

Ongoing work



Hierarchical integration

Ongoing work



Multi-output regression

Many thanks to colleagues

Technical University of Madrid

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The Cajal Institute

Benavides-Piccione, DeFelipe

NEUROANATOMY, NEUROLOGY AND BAYESIAN NETWORKS

Concha Bielza

Computational Intelligence Group
Artificial Intelligence Department
Technical University of Madrid, Spain

8th European Conference on Data Mining (DM2014)
8th International Conference on Intelligent Systems and Agents (ISA2014)
Lisbon, July 15, 2014